Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-4 and 9-26 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner reiterates his argument from the January 17, 2001 Office Action by stating that "one of skill in the art could not practice Applicant's invention without an undue burden because in view of Applicant's disclosure and the state of the art it was deemed unpredictable to practice Applicant's claimed invention." The Examiner also argued that:

> Since the state of the art does not recognize NRG-1 treatment for any form of congestive heart failure and...[Applicants] have no *in vivo* working examples demonstrating congestive heart failure treatment and the state of the art does not recognize that their *in vitro* data would reasonably correlate to *in vivo* treatment it would be unpredictable and require an undue amount of experimentation to practice Applicants' claimed invention.

Applicants respectfully traverse the rejection.

The M.P.E.P. § 2164.04 states that:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)...As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." (In re Marzocchi, 439 F.2d at 224, 169 USPQ at 370 (CCPA

1971).)

The Examiner fails to provide any evidence or reasoning that would suggest that Applicants' invention, directed to the treatment or prevention of congestive heart failure by the administration of a polypeptide encoded by a neuregulin gene, would be deemed unpredictable by the state of the art at the time the application was filed or that one skilled in the art would doubt that Applicants' *in vitro* data would reasonably correlate to *in vivo* treatment. Applicants submit that in addition to satisfying the test for enablement as required under M.P.E.P. § 2164, the invention would also be accepted by one skilled in the art. Applicants provide the following reasons for this conclusion. First, the specification provides the aortic stenosis model, a model that is well accepted by those skilled in the art as being a suitable experimental model for testing the efficacy of therapeutics for the treatment or prevention of congestive heart failure (see page 26 of the specification). Applicants provide considerable guidance in the specification regarding the use of this model to test the *in vivo* effects of a polypeptide encoded by a neuregulin for the treatment or prevention of congestive heart failure. Second, Applicants provide a detailed description of the effect of neuregulin polypeptides on the suppression of apoptosis and stimulation of cardiomyocyte proliferation *in vitro* (see page 36, line 17, through page 42, line 11). Third, Applicants provide a prophetic example that describes the use of a polypeptide encoded by a neuregulin gene to treat or prevent congestive heart failure *in vivo* using the aortic stenosis model, which, Applicants argue, correlates with

the *in vitro* effect of neuregulins on cardiomyocytes (see pages 48-49, of the specification). Applicants argue that the example provided is sufficiently detailed and clearly describes the required steps necessary to practice the invention without undue experimentation. Taken as a whole, Applicants argue that the specification provides considerable guidance that one skilled in the art can use to predictably practice the claimed invention without undue experimentation. The Examiner has provided no evidence to the contrary.

With reference to claim 10, the Examiner states that "if the Applicant can demonstrate by declaration by one of skill in the art or by recognition in the art that the disclosed aortic stenosis model would reasonably correlate to all forms of congestive heart failure..., the Examiner will reconsider the rejection." The M.P.E.P. § 2164.02 states:

> [T]he issue of correlation is...dependent on the state of the prior art...[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate...Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required...(see *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).)

In response to the Examiner's statement, Applicants submit that the aortic stenosis model is a well accepted model for heart failure (see, e.g., Routledge et al., J. Hum. Hypertens

15:659-667, 2001; Kim et al., ASAIO J., 47:667-672, 2001; Bocker et al., J. Cardiovasc. Pharmacol. 36:481-486, 2000; Walther et al., J. Invest. Surg. 13:327-331, 2000; Luo et al., Clin. Exp. Pharmacol. Physiol. 26:903-908, 1999; Bartunek et al., J. Am. Coll. Cardiol. 32:528-535, 1998; Chang et al., J. Clin. Invest. 100:1742-1749, 1997; Weinberg et al., Circulation 95:1592-1600, 1997; Keech et al., J. Invest. Surg. 10:295-304, 1997 (Abstract only; full-text to be provided shortly); Ishihara et al., Cardiovasc. Res. 26:580-585, 1992; and Iyengar et al., J. Thorac. Cardiovasc. Surg. 66:823-827, 1973; provided herewith). The prior art clearly indicates that this model is used to test therapeutic agents for their benefit in the treatment or prevention of congestive heart failure. Applicants also argue that those skilled in the field understand that congestive heart failure, identified by dilation of the left ventricular chamber, deterioration of systolic pump function, cardiomyocyte apoptosis, and deterioration of myocardial function (see, e.g., "ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary," *Journal of the American College of Cardiology* 38:2101-2113, 2001; provided herewith), can result from many different causes (e.g., those identified in instant claim 10), and that treatment that is demonstrated to be efficacious in treating or preventing heart failure using this model would reasonably correlate with heart failure caused by these other conditions.

Finally, Applicants argue that the specification clearly indicates that administration of a polypeptide encoded by a neuregulin gene promotes cardiomyocyte

survival and proliferation (see page 36, line 17, through page 42, line 11), which Applicants argue would be understood by one skilled in the art as likely to be "useful in inhibiting the progression of and/or protecting against congestive heart failure...[by] strengthen[ing] the pumping ability or completely prevent[ing] further deterioration of the heart by suppressing cardiomyocyte apoptosis." (See page 48, lines 11-17, of the specification.) Therefore, Applicants argue that besides recognizing that the aortic stenosis model reasonably correlates with heart failure caused by the conditions recited in claim 10, one skilled in the art would also recognize the benefit of treating or preventing heart failure using a polypeptide encoded by a neuregulin gene. Accordingly, Applicants respectfully request that the rejection of claims 1-4 and 9-26 under 35 U.S.C. § 112, first paragraph, may now be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for replying for two months, to and including March 9, 2002. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: March 11, 2002

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